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Dated 20 February 2004

Patents Form 1/77

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17JUL03 E823125-3 000245
P01/7700 0.00-0316657.6

Request for grant of a patent

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The Patent Office
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1.	Your reference	4-33283P1/HO 84	
2.	Patent application number *(The Patent Office will fill in this part)*	0316657.6	16 JUL 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number *(if you know it)*		
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic Compounds	
5.	Name of your agent *(If you have one)*		
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Craig McLean Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB	
	Patents ADP number *(if you know it)*	07181522002	

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	19
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 16 July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr
01403 32 3069

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Notes

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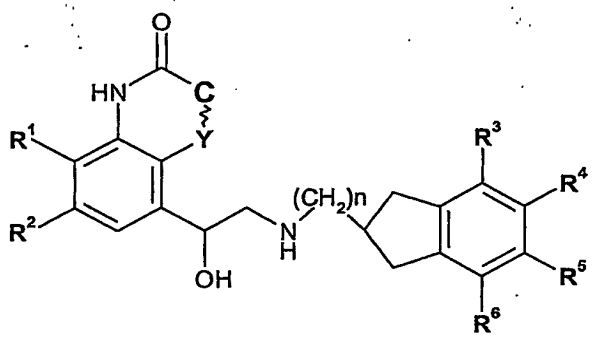
DUPLICATE

ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and use as pharmaceuticals.

The invention provides in one aspect a compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4; and

at least one of R^3, R^4, R^5 and R^6 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally and independently substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl,

the other or others of R^3, R^4, R^5 and R^6 being independently hydrogen, halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl.

Terms used in this specification have the following meanings:

"Optionally substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"Optionally and independently substituted" as used herein means where there are two or more moieties that may be optionally substituted as herein defined those moieties may be similarly or differently substituted.

"Halo" or "halogen" as used herein denotes a element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is chlorine or bromine.

"Aminocarbonyl" as used herein denotes amino attached through the nitrogen atom to a carbonyl group.

"C_1-C_{10}-alkyl" as used herein denotes straight chain or branched alkyl, which may be, for example, C_1 to C_{10} alkyl. Preferably C_1-C_{10}-alkyl is C_1-C_4-alkyl.

"C_1-C_{10}-alkoxy" as used herein denotes straight chain or branched alkoxy. Preferably C_1-C_{10}-alkoxy is C_1-C_4-alkoxy.

"C_3-C_{10}-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C_3-C_{10}-cycloalkyl is C_3-C_6-cycloalkyl.

"5- to 12-membered heterocyclic ring containing at least one ring heteroatom selected from nitrogen, oxygen and sulphur" as used herein denotes a monoheterocyclic, biheterocyclic or triheterocyclic group, which may be saturated or unsaturated, that has 5 to 12 ring atoms. Monoheterocyclic rings include furan, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiophene, thiadiazole, isothiazole, oxadiazole, pyridine, oxazole, isoxazole, piperidine, pyridine, pyrazine, pyridazine, pyrimidine, piperazine, morpholine, triazine, oxazine, thiazole, thiadiazole or tetrazole. Biheterocyclic rings include benzazole, benzimidazole, indazole, benzothiophene and benzothiazole. Preferably the 5- to 12-membered heterocyclic ring containing at least one ring heteroatom selected from nitrogen, oxygen and sulphur is a 5- to 9-membered heterocyclic ring containing at least one ring heteroatom selected from nitrogen, oxygen and sulphur. Preferred 5- to 12- membered heterocyclic rings include furan, thiophene, pyridine, thiazole, thiadiazole, tetrazole and benzothiophene. The 5- to 12-membered heterocyclic ring can be unsubstituted or substituted. Preferred substituents on the heterocyclic ring include halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy and C_3-C_{10}-cycloalkyl. Especially preferred substituents are halo and C_1-C_{10}-alkyl.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of the present invention are compounds of formula I where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0; and
at least one of R^3, R^4, R^5 and R^6 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally and independently substituted by halo or C_1-C_{10}-alkyl,
the other or others of R^3, R^4, R^5 and R^6 being hydrogen.

Especially preferred compounds of the present invention are compounds of formula I where
-C~Y- is -CH=CH-;
one of R^1 and R^2 is hydroxy and the other is hydrogen;
n is 0; and
at least one of R^3, R^4, R^5 and R^6 is a 5- to 9-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally and independently substituted by halo or C_1-C_4-alkyl,
the other or others of R^3, R^4, R^5 and R^6 being hydrogen.

The compounds of formula (I) are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid, sulfonic acids such as methanesulfonic acid or benzenesulfonic acid, and unsaturated monobasic aromatic acids such cinnamic acid, 4-methoxy cinnamic acid or 4-methyl cinnamic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

Compounds of formula I which contain acidic e.g. carboxyl groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline

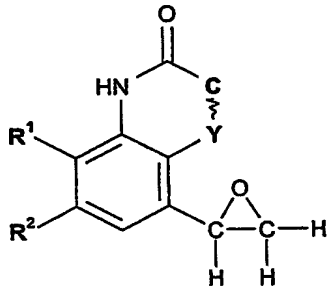
earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

In those compounds where there is an asymmetric carbon atom the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The present invention embraces individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

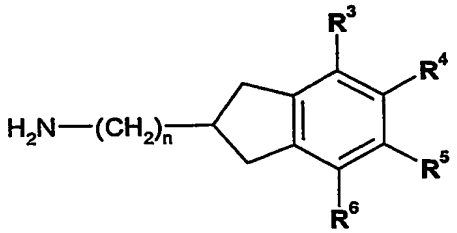
The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form. They can be prepared by a process comprising:

(i) (A) for the preparation of compounds of formula I reacting a compound of formula II



II

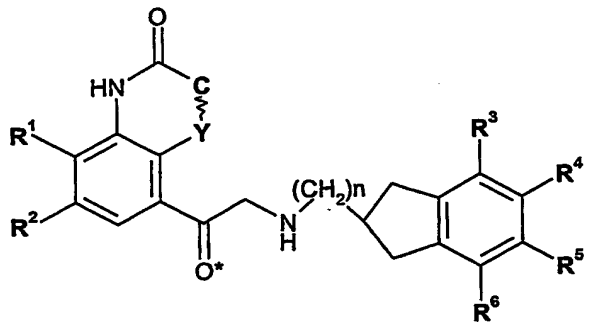
or a protected form thereof wherein -C~Y-, R^1 and R^2 are as defined in claim 1, with a compound of formula III



III

or a protected form thereof wherein R^3, R^4, R^5, R^6 and n are as hereinbefore defined; or

(B) reducing a compound of formula IV



IV

or a protected form thereof wherein -C~Y-, R^1, R^2, R^3, R^4, R^5, R^6 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

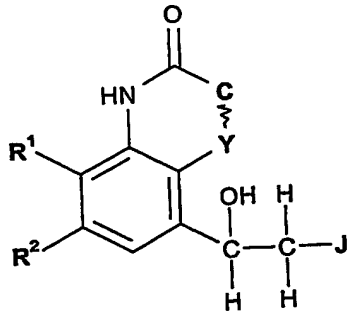
Process variant (A) may be carried out using known procedures for reacting epoxides with amines or analogously as hereinafter described in the Examples. The reaction is conveniently carried out without a solvent or in an inert solvent, for example an organic solvent such as 2-methoxyethyl ether. The reaction temperature is conveniently from 25°C to 200°C, preferably from 80°C to 190°C. The temperature may be achieved by conventional heating or by microwave irradiation.

Process variant (B) may be carried out using conventional methods, for example by hydrogenation using a suitable catalyst such as Pd/C or by reaction with sodium borohydride or a borane reducing agent under conventional conditions.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula II are known compounds or can be prepared by processes analogous to those used for the preparation of the known compounds, for example the procedures described in *J. Med. Chem.* 1987, 30, 1563.

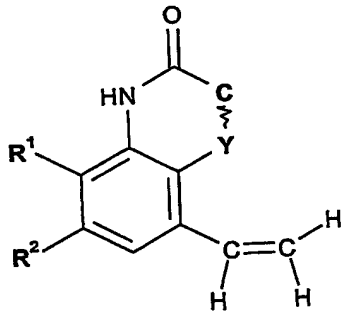
Compounds of formula II in which the carbon atom of the epoxide ring that is attached to the phenyl group is chiral may be prepared from a compound of formula V



V

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and J is a leaving atom or group, as described in international patent application WO 95/25104 or analogously as hereinafter described in the Examples.

Compounds of formula II may alternatively be prepared by epoxidation of a compound of formula VI

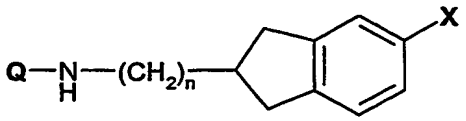


VI

or a protected form thereof -C~Y-, R^1 and R^2 are as hereinbefore defined, using conventional procedures.

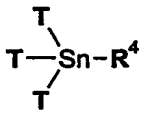
Compounds of formula III are known or may be prepared by methods analogous to those used for the preparation of the known compounds. The amine group may be protected by known methods.

Compounds of formula III where R^4 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl, and R^3, R^5 and R^6 are hydrogen, can be prepared by reacting a compound of formula VII



VII

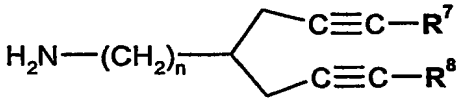
where n is as hereinbefore herein defined, X is a halogen such as bromine and Q is an amine- protecting group such as a tertiary-oxy-carbonyl group, with a compound of formula VIII



VIII

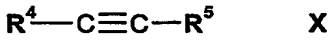
where R^4 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl and T is C_1-C_{10}-alkyl , for example butyl. The reaction can be carried out using the procedure described in *J. Am. Chem. Soc.* 2001, 123, 5918, or analogously as hereinafter described in the Examples. The reaction temperature is conveniently from 80°C to reflux temperature.

Alternatively, compounds of formula III where at least one of R^4 and R^5 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl, and the others of R^3, R^4, R^5 and R^6 are hydrogen, can be prepared by reacting a compound of formula IX



IX

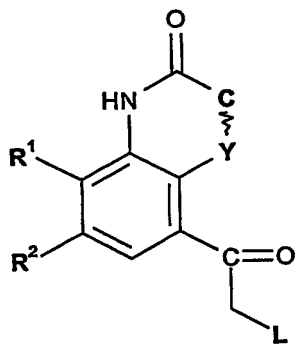
where R^a and n are as hereinbefore defined and R^7 and R^8 are each independently hydrogen or C_1-C_{10}-alkyl, with a compound of formula X



X

where at least one of R^4 and R^5 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl, and the other is hydrogen.

Compounds of formula IV are novel compounds which may be prepared by reaction of a compound of formula XI



XI

or a protected form thereof where -C~Y-, R^1 and R^2 are as hereinbefore defined and L is a halogen atom, preferably chlorine or bromine, with a compound of formula III as hereinbefore defined. The reaction may be carried out using known procedures, for example those described by Yoshizaki et al, *J. Med. Chem.* 1976, 19, 1138, or analogously as hereinafter described in the Examples.

Compounds of formula V are known or may be prepared by methods analogous to those used for the preparation of known compounds, for example those used in the Examples hereinafter.

Compounds of formula VI are known or may be prepared by known procedures.

Compounds of formula VII may be prepared as described in international patent application WO 96/23760 or by analogous procedures.

Compounds of formula VIII are known or may be prepared by known procedures.

Compounds of formula IX may be prepared as described in international patent application WO 96/23760 or by analogous procedures.

Compounds of formula X are known or may be prepared by known procedures.

Compounds of formula XI are known or may be prepared by known procedures, for example those disclosed in United States patent specification US 4460581 and German patent specification DE 3134590.

Where desired, the protection of any reactive group may be carried out at any appropriate stage in the above processes. The protecting group is suitably one used conventionally in the

art such as preferably benzyl or trifluoroacetyl and may be introduced and removed using a conventional procedure, for example using an amine-protective group as described in Protective Groups in Organic Synthesis, T. W. Greene, P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999. When a hydroxy group is protected by a benzyl group, the latter may be removed by catalytic hydrogenation in the presence of palladium on charcoal using conventional procedures, such as those used hereinafter in the Examples.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula I in free, salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free, salt or solvate form for use as a pharmaceutical. The compounds of formula I in free, salt or solvate form, hereinafter referred to alternatively as "agents of the invention", have good β_2-adreno-receptor agonist activity. The β_2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal strip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, *J. Pharmacol. Methods* 1989, 21, 71. The binding potency and selectivity for the β_2-adrenoreceptor relative to the β_1-adrenoreceptor can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S. J. Enna (editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β_2- or β_1-adrenoceptor, according to the procedure of B. January et al, *Brit. J. Pharmacol.* 1998, 123, 701.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β_2-adrenoreceptor, compounds of the Examples hereinbelow having K_i (β_2) values of the order of 0.1 to 1000 nM, having durations of action of the order of 1 to greater than 12 hours. Many of the compounds have binding selectivities for the β_2-adrenoreceptor relative to the β_1-adrenoreceptor from 1.5 to 500. The compound of

Example 1 has β_2 and β_1 binding potencies, measured by a classical filtration binding assay, represented by K_i values (β_2/β_1) (in μM) of 0.003 / 0.004.

Having regard to their β_2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β_2-adrenoreceptor. In view of their long acting selective β_2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, *J. Pharmacol. Toxicol. Methods* 1998, 39, 163, Hammelmann et al, *Am. J. Respir. Crit. Care Med.*, 1997, 156, 766 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β_2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a

recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

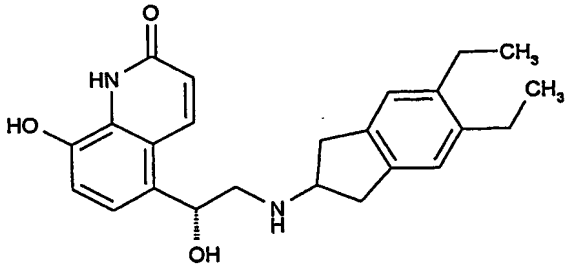
Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β_2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said agent of

the invention and said drug substance being in the same or different pharmaceutical composition. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, or steroids described in WO 0288167, WO 0212266, WO 02100879 or WO 0200679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), LTB4 antagonists such as those described in US 5451700, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo) and A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774 and A2b antagonists such as those described in WO 02/42298. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, but also those described in EP 424021, US 5171744 (Pfizer) and WO 01/04118 (Almirall Prodesfarma).

The agents of the invention are also useful as co-therapeutic agents for use in combination other beta-2 adrenoceptor agonists, for example as a rescue medication. Suitable beta-2 adrenoceptor agonists include salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International patent publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride.

Combinations of agents of the invention and steroids, PDE4 inhibitors, A2a agonists, A2b agonists or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, A2a agonists, A2b agonists, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

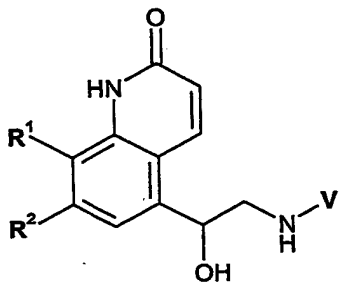
The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 μg.

The invention is illustrated by the following Examples.

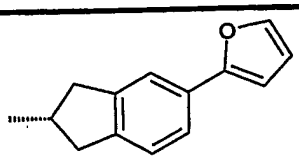
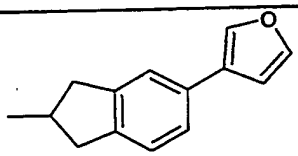
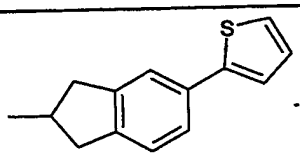
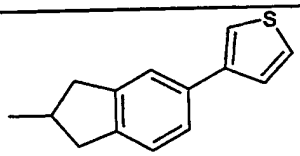
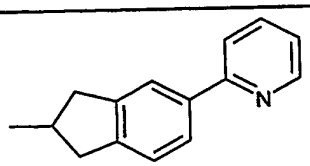
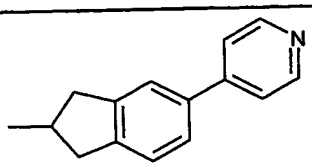
Examples

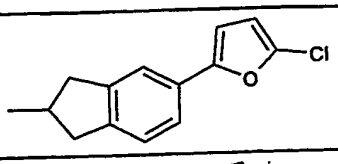
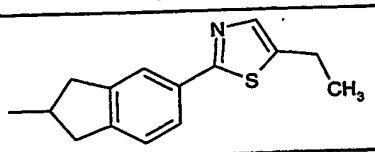
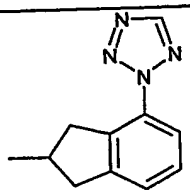
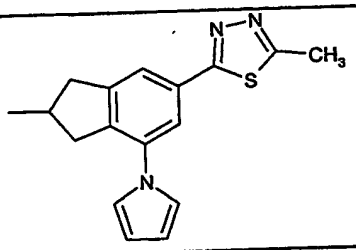
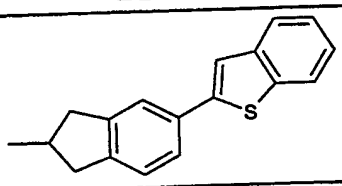
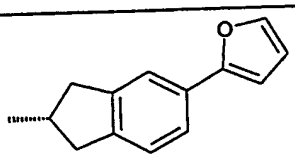
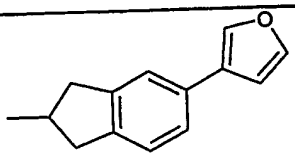
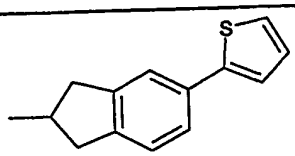
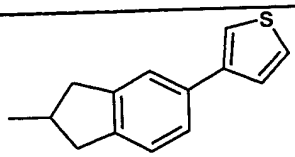
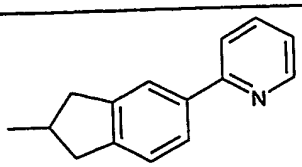
Especially preferred compounds of formula I are also compounds of formula XII

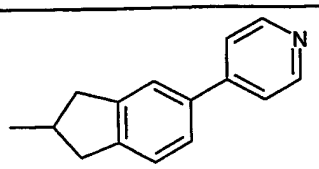
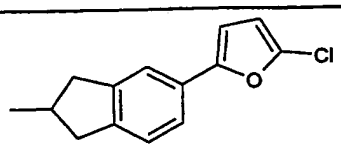
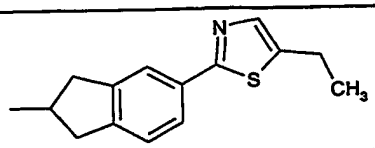
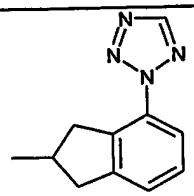
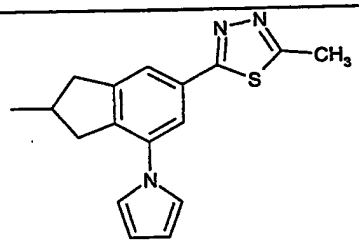
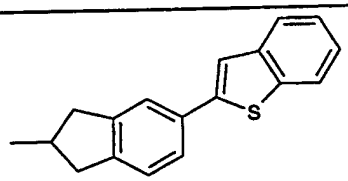


XII

wherein V is as shown in the following table, the method of preparation being described hereinafter. All compounds are prepared in the free form. 1H NMR spectra are recorded at 400 MHz in $CDCl_3$ unless otherwise noted. Mass spectra are obtained under electrospray ionisation conditions with LC gradient elution of 5% to 95% acetonitrile-water in the presence of 0.1% formic acid.

Ex	R^1	R^2	V	MH+
1	-OH	-H		403
2	-OH	-H		-
3	-OH	-H		-
4	-OH	-H		-
5	-OH	-H		-
6	-OH	-H		-

7	-OH	-H		-
8	-OH	-H		-
9	-OH	-H		-
10	-OH	-H		-
11	-OH	-H		-
12	-H	-OH		-
13	-H	-OH		-
14	-H	-OH		-
15	-H	-OH		-
16	-H	-OH		-

17	-H	-OH		-
18	-H	-OH		-
19	-H	-OH		-
20	-H	-OH		-
21	-H	-OH		-
22	-H	-OH		-

Example 1

5-[*R*-2-(*S*-5-(Furan-2-yl)indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one

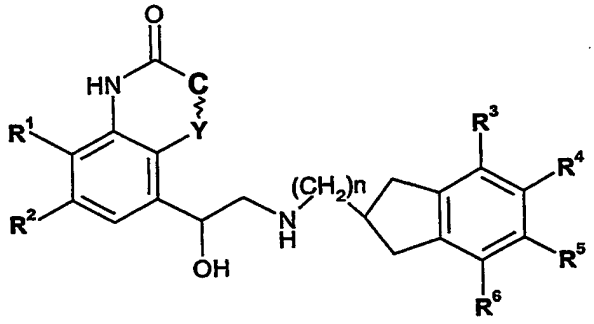
A solution of (*S*-5-bromo-indan-2-yl)-carbamic acid tert-butyl ester (WO 9623760, 0.790 g, 2.54 mmol) and 2-(tri *n*-butylstannyl)furan (0.880 ml, 2.79 mmol) in toluene is degassed by bubbling argon for 5 minutes, then tetrakis(triphenylphosphine)palladium (0.180 g, 0.15 mol) is added and the mixture heated to reflux for 1.5 hours. The solvent is evaporated and the crude product purified by flash chromatography, eluting with 1:1 CH_2Cl_2-isohexane to afford (*S*-5-(furan-2-yl)indan-2-yl)-carbamic acid tert-butyl ester, MH+ 300.

Examples 13 to 22

The compounds of these Examples are prepared using procedures that are analogous to those described in Example 12 using the appropriate carbamic acid tert-butyl ester or amine.

CLAIMS

1. A compound of formula I



I

in free or salt or solvate form, where

-C~Y- denotes -CH_2-CH_2-, -CH=CH- or -CH_2-O-;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4; and

at least one of R^3, R^4, R^5 and R^6 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally and independently substituted by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl,

the other or others of R^3, R^4, R^5 and R^6 being independently hydrogen, halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl.

2. A compound according to claim 1, where

-C~Y- is -CH=CH-;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is 0; and

at least one of R^3, R^4, R^5 and R^6 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally and independently substituted by halo or C_1-C_{10}-alkyl,

the other or others of R^3, R^4, R^5 and R^6 being hydrogen.

3. A compound according to claim 2, where

-C~Y- is -CH=CH-;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is 0;

at least one of R^3, R^4, R^5 and R^6 is a 5- to 9-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally and independently substituted by halo or C_1-C_4-alkyl,
the other or others of R^3, R^4, R^5 and R^6 being hydrogen.

4. A compound according to claim 1 substantially as herein described with reference to any one of the Examples.

5. A compound according to any one of the preceding claims for use as a pharmaceutical.

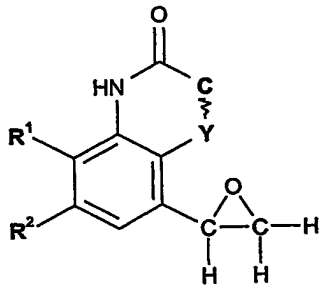
6. A pharmaceutical composition comprising a compound according to any one of the preceding claims, optionally together with a pharmaceutically acceptable carrier.

7. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of a condition which is prevented or alleviated by activation of the β_2-adrenoreceptor.

8. Use of a compound according to any one of claims 1 to 4 for the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

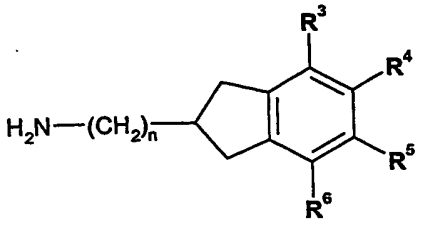
9. A process for the preparation of a compound of formula I as claimed in claim 1 in free or salt or solvate form comprising:

(i) (A) for the preparation of compounds of formula I reacting a compound of formula II



II

or a protected form thereof wherein -C~Y-, R^1 and R^2 are as defined in claim 1, with a compound of formula III

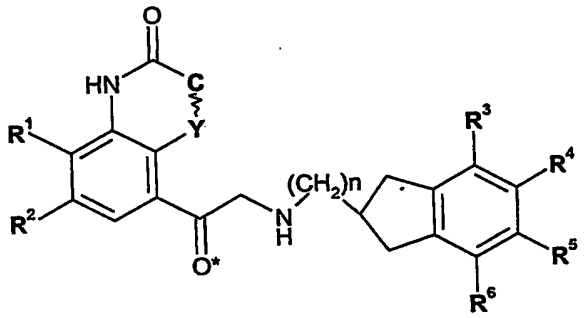


III

or a protected form thereof wherein R^3, R^4, R^5, R^6 and n are as hereinbefore defined;

or

(B) reducing a compound of formula IV

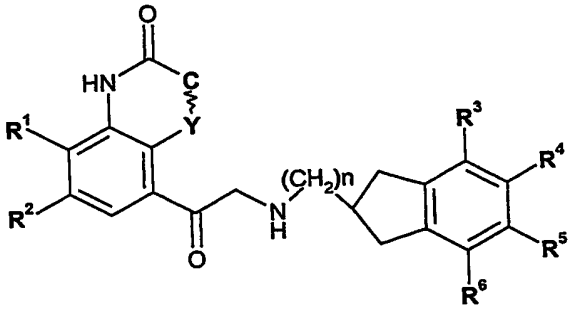


IV

or a protected form thereof wherein -C~Y-, R^1, R^2, R^3, R^4, R^5, R^6 and n are as hereinbefore defined, to convert the indicated keto group into -CH(OH); and

(ii) recovering the resultant compound of formula I in free or salt or solvate form.

10. A compound of formula IV



IV

in free or salt or solvate form, where

-C~Y- denotes $-CH_2-CH_2-$, -CH=CH- or $-CH_2-O-$;

one of R^1 and R^2 is hydroxy and the other is hydrogen;

n is an integer from 0 to 4; and

at least one of R^3, R^4, R^5 and R^6 is a 5- to 12-membered heterocyclic ring wherein at least one of the ring atoms is nitrogen, oxygen or sulphur, that ring being optionally substituted

by halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl,
the other or others of R^3, R^4, R^5 and R^6 being independently hydrogen, halo, cyano, hydroxy, carboxy, aminocarbonyl, nitro, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy or C_3-C_{10}-cycloalkyl.